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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/801,087	03/15/2004	Rudolph E. Tanzi	M0765.70052US01	2184

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EXAMINER

BALLARD, KIMBERLY A

ART UNIT	PAPER NUMBER
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1649

DATE MAILED: 05/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/801,087	Applicant(s) TANZI ET AL.	
	Examiner Kimberly A. Ballard	Art Unit 1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 April 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3, 5, 7, 8, 12-14, 16, 18, 19, 23, 26, 28, 31-34, 36, 38 and 39 is/are pending in the application.
- 4a) Of the above claim(s) 1-3, 5, 7, 8, 12-14, 16, 18, 19, 32-34, 36, 38 and 39 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 23, 28 and 31 is/are rejected.
- 7) ☒ Claim(s) 26 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment filed 24 June 2004 has been fully considered and entered. Applicant has canceled claims 4, 6, 9-11, 15, 17, 20-22, 24, 25, 27, 29, 30, 35, 37, and 40-51. Claims 1-3, 5, 7, 8, 12-14, 16, 18, 19, 23, 26, 28, 31-34, 36, 38, and 39 are pending.

Election/Restrictions

Applicant's election without traverse of Group II, claims 23, 26, 28, and 31, drawn to a method for identifying compounds that modulate caspase activation-induced stabilization of a secretase pathway associated protein, in the reply filed on 14 April 2006 is acknowledged.

Claims 1-3, 5, 7, 8, 12-14, 16, 18, 19, 32-34, 36, 38 and 39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 14 April 2006.

Claims **23, 26, 28, and 31** are under examination in the instant office action.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states,

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"the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23, 28, and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying compounds that modulate caspase activation-induced stabilization of presenilins, nicastrin/Aph2, BACE, Aph1a, and Pen-2, *does not reasonably provide enablement for* identifying compounds that modulate caspase activation-induced stabilization of all secretase pathway associated proteins as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

The claims are broadly drawn to a method for identifying compounds that modulate caspase activation-induced stabilization of a secretase pathway associated protein, wherein the method requires measuring the stability of the secretase pathway associated protein.

The specification discloses on p. 14 that a "secretase pathway associated protein" is a protein that is involved in the production of A β from amyloid precursor protein (APP) and includes, but is not limited to: presenilins (including PS1 and PS2), nicastrin/Aph2, Aph1a, Pen-2, and BACE. The specification also discloses working examples of caspase-induced stabilization of presenilin-1 (PS1), BACE, nicastrin, Pen-2, and Aph-1 (Examples 4-6). Hence, the stability of certain γ -secretase proteins such as PS1, nicastrin, Pen-2 and Aph-1, and the β -secretase BACE appear to be influenced by caspase activation. However, the list of secretase molecules provided in the instant application is far from complete.

The specification's disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The specification does not provide clear guidance as to additional secretase pathway associated proteins capable of use in the identification of specific stabilization modulators. For example, Wilson et al. (*J. Neurosci Res*, 2003; **74**: 361-369) suggest that in addition to the presenilins, there may be multiple, distinct γ -secretases based on the observation that certain γ -secretase inhibitors can differentially block production of A β 40 relative to A β 42, or even stimulate production of A β 42 while inhibiting A β 40 (see in particular, p. 363-364). Moreover, it is reported that conversion of full-length

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presenilin (PS) into functional PS N-terminal fragment (NTF) and C-terminal fragment (CTF) is mediated by an unknown protease activity named presenilinase (see Xia W. *Drug News Perspect.* 2003 Mar; **16**(2): 69-74). Further, Dewachter and Van Leuven (*Lancet*, 2002; **1**: 409-416) indicate that in addition to the β - and γ -secretases disclosed in the instant application, the α -secretases ADAM10 and ADAM17 (TACE) are also involved in proteolytic processing of APP (in particular, see p. 410). Dewachter and Van Leuven also note that the enzymatic activity of ADAM10 and ADAM17/TACE is coordinated by a furin-type pro-protein convertase (see p. 411, 1st column and Figure 4, p. 412). A furin-like protein also regulates the proteolytic processing and activity of BACE (see Figure 4, p. 412). Thus, the as-yet-undefined γ -secretases suggested by Wilson et al., the presenilinase enzyme reported by Xia, and the α -secretases, ADAM10 and ADAM17, and furin-like protein described by Dewachter and Van Leuven would all constitute "secretase pathway associated proteins" based on the definition *supra*. As such, the state of the prior art demonstrates the relative unpredictability of deciphering the particular molecules involved in secretase processing of APP.

Accordingly, one skilled in the art would first have to reliably identify additional secretase pathway associated proteins such as those indicated in the art and then determine which, if any, of these proteins are stabilized by caspase activity before the artisan could practice the method of determining modulators of this activity. Thus, undue experimentation would be required to practice the invention as claimed in its current scope.

In summary, it would not be expected that one of ordinary skill in the art could successfully use the instant invention as broadly claimed for the reasons stated above. When combined with the lack of guidance from the instant specification on secretase pathway associated proteins and the state of the art which suggests unpredictability in the identification of additional secretase proteins involved in APP processing, the claims merely represent an invitation to experiment to discover how to use Applicants' invention.

Claims 23, 28, and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Factors to be considered when determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. (Written description guidelines, Federal Register, vol. 66, no. 4, January 2002, 9.1106, column 2).

The claims are broadly drawn to a method for identifying compounds that modulate caspase activation-induced stabilization of a secretase pathway associated protein, wherein the method requires measuring the stability of the secretase pathway

associated protein. Because the identity of the secretase pathway associated protein must be known in order to measure its stability and thereby use the method in its full scope, and because secretase pathway associated proteins comprise a multitude of molecules, the claims thus encompass a method of using a genus of secretase pathway associated proteins.

A description of a genus may be achieved by means of a recitation of a representative number of members, defined by structure and/or function, falling within the scope of the genus, or of a recitation of structural and/or functional features common to the genus, which features constitute a substantial portion of the genus. Applicant has defined the term “secretase pathway associated protein” as a protein that is involved in the production of A β from amyloid precursor protein (APP) and includes, but is not limited to: presenilins (including PS1 and PS2), nicastrin/Aph2, Aph1a, Pen-2, and BACE (p. 14). Thus, the scope of the claims includes the use of a genus of molecules – beyond the six proteins listed in the instant specification – for the identification of specific stabilization modulating compounds. Applicant has not provided guidance as to any particular common structure, function, or other characteristic that would result in the required stabilization and thus identify other members of the genus that could be used in the methods. As noted in the art *supra*, there are many additional identified and unidentified molecules that are involved in secretase proteolytic processing of APP. There is no means by which the artisan, given any of these proteins, would know whether it was a member of the genus that could be used in this assay or not. The instant disclosure of the six exemplary proteins involved

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in the production of A β from APP does not adequately support the scope of the claimed genus of secretase pathway associated proteins, which encompasses a substantial variety of subgenera.

The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Moreover, given the unpredictability of the identification and characterization of secretase associated proteins as noted *supra*, and the fact that the specification fails to provide objective evidence of any other proteins that are stabilized by caspase activity and thus are indeed species of the claimed genus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to support the method of identifying modulators of such a genus. Thus, Applicant was not in possession of the claimed genus.

Claim Objections

Claim 26 is objected to because it depends from rejected claim 23.

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kimberly Ballard, Ph.D.
Art Unit 1649
May 2, 2006


JANET L. ANDRES
SUPERVISORY PATENT EXAMINER